Gender-specific modifiable factors of bone stiffness in Korean population: the KGRC Study

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Gender-specific modifiable factors of bone stiffness in Korean population: the KGRC Study

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TABLE OF CONTENTS

ABSTRACT ----------1

I. INTRODUCTION ----------3

II. MATERIALS AND METHODS ----------8

A. Setting and study subjects ----------8

B. Questionnaire ----------9

C. Anthropometry measurement and definition ----------10

D. Bone measurements ----------11

E. Statistical analysis ----------12

III. RESULTS ----------13

A. General characteristics of the study population ----------13

B. Factors affecting the bone stiffness among men ----------15

C. Factors affecting the bone stiffness among women ----------19

IV. DISCUSSION ----------24

REFERENCES ----------32

LIST OF FIGURES

Fig. 1 The distribution of subjects in KGRC Study ----------9

Fig. 2 Mean of bone stiffness in men and women by 5-year age groups ----------14

LIST OF TABLES

Table 1. Studies of calcaneal QUS in more than 500 adults recruited from general populations ----------7

Table 2. Social-demographic characteristic of the study group ----------14

Table 3-1. Distribution of potential risk factors by age in men --------15

Table 3-2. Mean bone stiffness values of potential risk factors by age in men ----------17

Table 3-3. Multiple linear regression analysis for bone stiffness in men ----------18

Table 4-1. Distribution of potential risk factors by menopause status in women ----------19

Table 4-2. Mean bone stiffness values of potential risk factors by menopause status in women ----------21

Table 4-3. Multiple linear regression analysis for bone stiffness in women ----------23

ABSTRACT

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Background & Purpose: Bone stiffness, one of the quantitative ultrasound (QUS) parameters, has been a recent focus for evaluation and prediction of osteoporosis and fracture risks worldwide. This study was performed to investigate the modifiable factors of bone stiffness in a large sample of the Korean population.

Methods: Data were drawn from the Korean Genomic Rural Cohort (KGRC) Study, which is an ongoing population-based study of adults from five regions. A total of 7,066 participants (2,970 men and 4,096 women) aged 40 to 70 years who has never been treated with osteoporosis and/or previous fractures were analysed. Index of bone stiffness was expressed as a percentage of young normal values, which was measured by calcaneus QUS device (Lunar Model A-1000 Plus, Lunar Co., Madison, WI, USA). Multiple regression analysis was conducted to estimated the potential risk factors of bone stiffness. SPSS for Windows (version 12.0) was used for all statistical analyses.

Results: At all ages, mean bone stiffness is lower in women than in men and the annual decreasing rate of bone stiffness in women was

2.6-fold of that in men (0.447% per year, and 0.171% per year, respectively). In multivariate regression analysis of men aged 40 to 59, BMI, time spent exercise and dietary protein intake were significantly correlated with bone stiffness, and men at aged 60 to 70, BMI, lifetime tobacco smoking and time spent exercise were significantly correlated with bone stiffness. Meanwhile, in women, BMI, time spent exercise and dietary protein intake in premenopausal, and years since menopause, BMI, estrogen replacement therapy and number of parity in postmenopausal were significantly correlated with bone stiffness.

Conclusions: The level of bone stiffness is poor among adults in rural Korean and it was associated with many risk factors for further osteoporosis and fractures. Early lifestyle modifications, such as healthy diet, optimal weight control, avoid smoking and exercise are recommended interventions.

Key word: modifiable factors, bone stiffness, quantitative ultrasound, Korean population

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I. INTRODUCTION

Osteoporosis is a progressive systemic disease characterized by low bone mass and deterioration of bone tissue leading to bone fragility and fracture. Around one in six women over the age of 50 develops an osteoporotic fracture at some point during her lifetime. The calculated lifetime risk of an osteoporotic fracture in men is 13.5% at the age of 50 years and 25.6% at the age of 60 years. Up to 20% of elderly patients will die within 1 year of the fracture event and up to 50% lose their independence, often requiring institutionalization (Javaid and Holt, 2008). The severe outcomes resulting from osteoporotic fractures not only affect the lives of elderly individuals, but also create tremendous social and economic burdens for the country. Moreover, resultant fractures in the spine or hip cause disability and increase socioeconomic costs (Barrett-Connor et al., 1995).

In recent decades, osteoporosis and associated fractures has become a

growing public health concern in Korea as the elderly population expands rapidly. In 2007, the proportion of the Korean aged 65 years or older was 8.7% of the whole population, and it is expected to reach 15.1% in 2020 (Korea National Statistical Office, 2007). This trend indicates that osteoporosis-related fractures may become a major health problem in Korea. A total of 7,632 males and 16,066 females suffered from hip fractures according to National Health Insurance Corporation data in the year 2005. The age- and gender- adjusted incidence rates of hip fracture among men and women over 40 years of age, estimated from the Health Insurance Review Agency Database, were 106.0/100000/year and 156.9/100000/year, respectively (Lim et al., 2008). Strong efforts, recently undertaken to understand the factors that influence bone health in the general population, may lead to the development of strategies for better prevention of osteoporotic fractures.

At present, several methods are used to determine bone status, of which the most common are dual-energy X-ray absorptiometry (DXA) and quantitative ultrasound (QUS). The central DXA, predicts fracture risk by measuring bone mineral density (BMD) and has become recognized as the gold standard for predicting osteoporosis. QUS technology of bone measurement has been recently drawing increasing attention because compared with DXA, it is a simpler measuring method of bone screening as it has advantages of low cost, simplicity of use, portability, and absence of radiation exposure (Christiansen, 1995; Yamazaki et al., 1994). The QUS measurements have been proposed as they provide not only the BMD but also the structural properties of bone as predictors of bone strength (Sosa et al., 2002; Gluer et al., 1994; Kaufman and Einhorn, 1993). The index of bone

stiffness, one of the QUS parameters, has been a recent focus for evaluation and prediction of osteoporosis and fracture risks worldwide (Heldan et al., 2000; Hoshino et al., 1996; Schott et al., 1995; Yamaguchi et al., 2000). In addition, earlier studies have shown that it could predict fracture as effectively as the BMD does in both men and women (Hans et al., 1996; Gonnelli et al., 2005). Therefore, we used QUS rather than DXA. Moreover, Lees and Stevenson (1993) reported that calcaneal bone stiffness has the best precision when the effective range of measurements is taken into account.

It is well known that genetic factors influence peak bone mass, but many environmental factors also play a role in altering genetic effects (Livshits et al., 2004; Eisman, 1999; Smith et al., 1973). There are a number of important clinical risk factors for fracture among Caucasian women, including low body weight, history of fracture, family history of fracture, smoking, use of glucocorticoid steroids and physical inactivity (Genant et al., 1999). However, numerous studies indicate that there are considerable differences in BMD and fracture risk among different racial or ethnic groups. Asians have been suggested to have lower BMD than Caucasians because of smaller body size and low calcium intake (Bhudhikanok et al., 1996). Meanwhile, since older women suffer more from osteoporosis than older men as a result of accelerated bone loss during their estrogen-deficient perimenopausal period, many studies on osteoporosis concentrated mainly on women. On the other hand, osteoporotic fractures in men also confer a major health problem. From the literature review, there is a paucity of studies investigating gender-specific risk factors of poor bone status among Asian people, particularly in Korea (see the Table 1).

The objectives of the current study were to examine bone strength measured by bone stiffness values, and to explore the factors that may influence bone stiffness in the Korean men and women respectively.

Table 1. Studies of calcaneal QUS in more than 500 adults recruited from general populations

Country	Men	Women	Author, date	Change in bone stiffness units per year(%)	
	Age range	Age range		Men	Women
Japan		1421 19-84years	Yamaguchi et al., 2000		-0.490
Japan①		841 mean=55years	Fukuharu et al., 2001		-0.430
Japan		573 ≥40years	Zhang et al., 2003		-0.445
China②		2498 ≥10years	Liu et al., 2006		-0.265
China③	568 10-82years	725 10-83years	Liu et al., 2006	-0.158	-0.308
Korea		552 ≥56years	Kim et al., 2000		NA
Lebannese		4320 20-79years	Wehbe et al., 2003		-0.303
Italy④	4981 60-80years	6811 40-80years	Adami et al., 2003	-0.170	-0.631
Turkey⑤	1389 18-89years	6767 18-89years	Durmaz et al., 2006	-0.250	-0.590
Taiwan⑥	7548 16-89years	9314 14-92years	Lin et al., 2001	-0.320	-0.504
Spain	1138 ≥18years	1451 ≥18years	Sosa et al., 2002	-0.204	-0.474
Sweden	422 20-79years	534 20-79years	Grahn et al., 2004	-0.334	-0.381

① Excluding previous gynecological or gastrointestinal operations. ②Excluding major systemic disorders or diseases affecting bone metabolism, such as the heart, kidney, liver, thyroid, parathyroid, adrenal, diabetes mellitus, hematologic disease, or a history of malignant tumor, and so forth. ③Excluding major systemic disorders or diseases affecting bone metabolism, such as disease of the heart, kidney, liver, thyroid, parathyroid, adrenal, diabetes mellitus, hematologic disease, or a history of malignant tumor, etc., and the subjects were taking any agent known to affect bone metabolism, such as steroids, vitamin D, calcium, calcitonin, thiazides, thyroid hormone, biphosphouate, barbiturates or anti-convulsant medication. ④Excluding any premenopausal women and postmenopausal women with hormone replacement therapy for more than a year. ⑤Excluding any medical treatment or any disease known to affect bone metabolism. ⑥ Excluding diabetes mellitus or other endocrine disorders. NA, bone mass was assessed by T-score, not by bone stiffness.

II. MATERIALS AND METHODS

A. Setting and study subjects

This study was conducted as a part of the Korean Genomic Rural Cohort (KGRC) Study, a prospective population-based cohort study among men and women aged 40 to 70 years old, focused on hypertension, diabetes, osteoporosis, respiratory disease and metabolic syndrome. This study was approved by the Institutional Review Board of Yonsei University Wonju College of Medicine. The baseline examination of the KGRC Study was carried out in rural areas of Wonju, Pyeongchang, Gangreung, Geumsan, and Naju (Fig. 1) from October 2005 to January 2008 and subjects were asked to participate in this study using the media, conferences, telephone calls etc. A total of 10,110 persons, who were looking healthy and ambulatory, visited the research center, and most of whom were engaged in farming activities. The informed consent was obtained from each participant before the start of the study. Of them, those being treated for osteoporosis and/or who had previous fracture were excluded to eliminate the possible effect of osteoporosis medication. Finally, 7,066 participants (2,970 men and 4,096 women) were analyzed.

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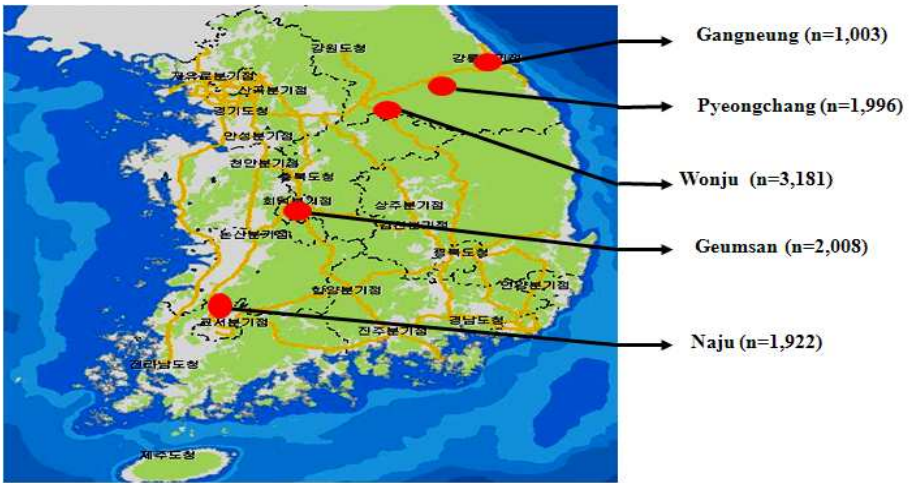

Fig. 1 The distribution of subjects in KGRC Study

B. Questionnaire

All subjects were asked a detailed questionnaire on socio-demographic, health related behavioral, dietary and medical data. Socio-demographic data included gender, age, marital status, educational level, and occupation. Health related behavioral data included physical activity, tobacco smoking, and alcohol consumption. Dietary data were obtained using a semiquantitative food-frequency questionnaire (FFQ) that listed 103 food items generally consumed daily by Koreans. Medical data included previous or current history of disease, such as fracture, stroke, angina, myocardial infarction, hypertension, clinical thyroidism, diabetes, glaucoma, chronic liver disease, gastric disease, pulmonary disease, Parkinson's disease, rheumatoid arthritis, psychiatric illness, allergic disease, and cancer. For women, an additional reproductive questionnaire was administered to collect data on menstrual and reproductive history, including age at menarche, history of

menstrual dysfunctions, age at menopause, number of pregnancies, as well as current and past postmenopausal estrogen use. After completing the questionnaires by themselves, a trained technician helped those who were unable to fully understand the questions.

C. Anthropometry measurement and definition

In each subject, body weight and height were measured with light clothing without shoes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2) and classified according to the guideline of the World Health Organization: underweight (<20), normal (20 to <25), overweight (25 to <30) and obese (≥30). The participants were then divided into three categories according to their smoking behavior. Subjects were defined as current smokers (subjects who had smoked at least 1 cigarette/day for the previous 1 year), former smokers (subjects who had stopped smoking for at least 3 months), and never-smokers. Lifetime tobacco smoking was expressed in terms of pack-years, the product of 1 pack of 20 cigarettes and the number of years of smoking. The alcohol drinker was defined as one who drinks alcoholic beverages at least once a month. For current drinkers were asked how often, on average over the past year, they consumed each beverage. We calculated total alcohol intake by multi-plying the average consumption of each beverage by the alcohol content of the specified portion size (13.0g for makkolli, 10.0g for soju, 7.0g for beer, 8.5g for wine, and 9.5g for whisky) and summing across beverages. These figures were based on the average concentrations of alcohol in various types of beverages set by the

Government Alcohol Agency in Korea. Level of total alcohol consumption was grouped according the Korean Academy of Addiction Psychiatry guidelines for alcohol drinking. The academy recommends that "light to moderate drinking" were consumed less than 24g/day in men and less than 15g/day in women, respectively. Smoking and alcohol drinking habits of female subjects were divided into two groups, i.e., non- and smoker or drinker group, because the number of ex-smoker and ex-drinker was limited. Physical activity was categorized as none, between 1 and 4 times/week and more than 5times/week. Consistent with their age, over 75% reported relatively low-intensity exercise such as stretching exercise, walking slowly. Female subjects who menstruated regularly at the time of the survey were judged to be premenopausal and those who had entered menopause at least 12 months prior to the survey were judged postmenopausal. Four hundred ten women who menstruated irregularly within 11 months were judged missing data.

D. Bone measurements

Bone mass was assessed by bone stiffness using the Achilles ultrasonometer (Lunar Model A-1000 Plus, GE Lunar Co., Madison, WI, USA) at the right calcaneus. The ultrasound system consists of two sound transducers (emitting and receiving) were faced with elastomer pads. Contact between the heel and the emitting and receiving transducer of the ultrasound was achieved with ultrasonic coupling gel. The ultrasound signal is emitted from one transducer and transmitted to the second transducer. After the signal is digitized and stored, the data

are sent to a computer for automated analysis. The index of bone stiffness, was expressed as a percentage of young normal values and obtained by a mathematical combination of broadband ultrasound attenuation (BUA) and speed of sound (SOS) using the following formula: Bone stiffness = 0.67 × BUA + 0.28 × SOS −420 (Hans et al., 1998). Calcaneal bone stiffness correlates highly ($r<0.85$) with the BMD of the purely cancellous bone and accuracy is high (Rackoff and Rosen, 1998). Quality control checking was performed daily, prior to testing the subjects by scanning phantoms provided by the manufacturer.

E. Statistical analysis

All statistical procedures were performed with SPSS version 12.0 (SPSS, Chicago, USA). Descriptive statistics was presented as means with standard deviation (SD) or proportions and Student's t-test and analysis of variance (ANOVA) with Scheff'e's post hoc test were used for comparison of mean bone stiffness values according categorical variables. Further, we built multiple linear regression analysis to check the effect factors on bone stiffness.

III. RESULTS

A. General characteristics of the study population

Descriptive characteristics of the study population are shown in Table 2. Majority of subjects were aged 50 to 70 years old and farmers, and more than half had a low level of education.

Bone stiffness declined with increasing age in both men and women. At any age range, bone stiffness was higher in men than in women and the mean decreasing rate of bone stiffness in men was 0.171% per year and 0.447% per year in women. The acceleration of bone loss was visible over the age of 60 years in men and over the 50 years in women, which may be as a result of menopause (Fig. 2). Therefore, we grouped the subjects into four groups; two groups of men (aged 40 to 59 years old men, 60 to 70 years old men) and two groups of women (premenopausal women, postmenopausal women).

Table 2. Socio-demographic characteristics of the study group

number(%)

	Men (n=2970)	Women (n=4096)
Age(years)		
40-49	625 (21.0)	1311 (32.0)
50-59	1061 (35.7)	1525 (37.2)
60-70	1284 (43.2)	1260 (30.8)
Occupation		
non/housewife	293 (9.9)	1287 (31.5)
worker	705 (23.9)	811 (19.9)
farmer	1954 (66.2)	1982 (48.4)
Education		
elementary school or less	339 (11.5)	1034 (25.2)
middle school	1631 (55.2)	2270 (55.4)
high school/college	987 (33.4)	774 (18.9)
Married		
single	158 (5.4)	650 (16.0)
married	2792 (94.6)	3422 (84.0)

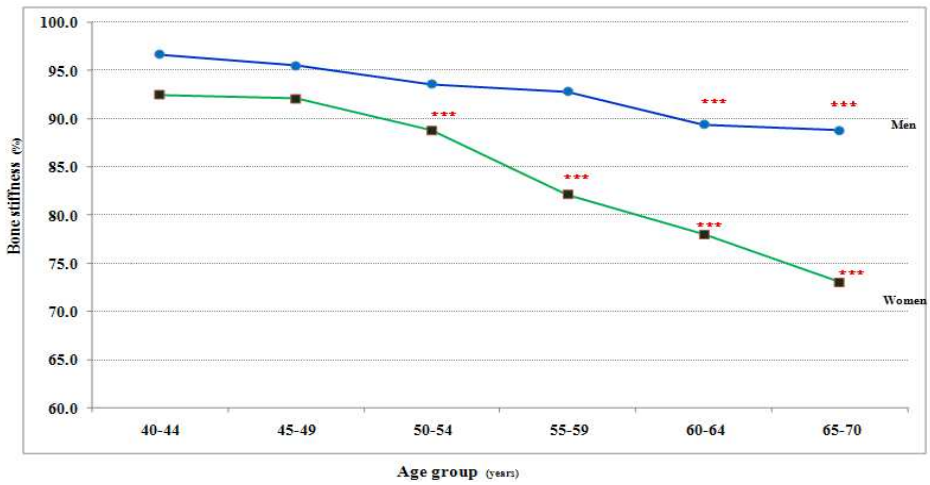

Fig. 2 Mean of bone stiffness in men and women by 5-year age groups

*** significantly ($p<0.001$) different from the 40-44 year age group

B. Factors affecting the bone stiffness among men

Table 3-1 shows baseline characteristics of the two groups in men. Mean BMI, alcohol consumption, dietary calcium and protein intake were significantly higher in the group of younger men, while the prevalence of any chronic disease and total amount of tobacco smoked were significantly higher in the elder men.

Table 3-1. Distribution of potential risk factors by age in men

	40≤age≤59 (*n*=1686)	60≤age≤70 (*n*=1284)
BMI(kg/m^2)***	24.6±3.20	23.8±2.99
Any chronic disease(%)***	56.5	66.6
Current smokers(%)	40.7	31.5
Smoking(pack-years)***	18.1±17.4	22.4±23.3
Current drinkers(%)	68.1	57.6
Alcohol consumption(g/day)***	33.3±55.6	27.7±48.4
Regular exercise(%)*	27.0	27.3
Dietary calcium intake(mg/day)	420.3±287.8	414.3±259.2
Dietary protein intake(g/day)***	62.4±28.4	57.0±25.8

* p<0.05; ** p<0.01; ***p<0.001

Table 3-2 shows the mean bone stiffness values of potential risk factors by age in men. There were positive linear trend of BMI and time spent exercise with bone stiffness, but there were no significant differences in bone stiffness of subjects by the level of dietary intake of calcium and protein. Smoking seems to be a significant factor of the low bone stiffness, while the subject who drank light to moderate amounts of alcohol had higher level of bone stiffness than those who did not drink, and these phenomena were more prominent in the elderly men.

Table 3-3 shows the results of multivariate regression analysis in men. BMI, time spent exercise and dietary protein intake in aged 40 to 59, and BMI, lifetime tobacco smoking and time spent exercise in aged 60 to 70 were significantly correlated with bone stiffness.

Table 3-2. Mean bone stiffness values of potential risk factors by age in men

Variable	Men(40≤age≤59)			Men(60≤age≤70)		
	n	Mean±SD	*P*	*n*	Mean±SD	*P*
BMI						
underweight	99	86.6±13.4		115	85.7±16.8	
normal	834	93.5±15.4	0.000	697	88.4±16.0	0.000
overweight/obese	702	96.3±15.9		432	91.5±16.1	
Any chronic disease						
no	715	95.1±16.2	0.042	412	88.5±16.4	0.431
yes	919	93.5±15.3		824	89.3±16.1	
Smoking status						
no	467	95.5±16.4		422	91.7±16.0	
ex	510	95.0±15.3	0.005	436	89.7±15.7	0.000
current	669	92.7±15.5		394	85.7±16.4	
Smoking(pack-years)						
0	467	95.5±16.4		422	91.7±16.0	
0< ≤20	437	93.7±15.9	0.105	219	87.7±14.0	0.000
>20	743	93.7±15.1		611	87.8±16.9	
Drinking status						
no	364	92.5±15.8		359	88.7±16.6	
ex	155	94.3±13.3	0.064	171	88.9±16.7	0.819
current	1126	94.8±16.0		721	89.4±15.9	
Alcohol consumption(g/day)						
0	519	93.1±15.1		530	88.8±16.7	
≤24	429	94.5±16.2	0.205	295	91.1±15.7	0.034
>24	632	94.6±16.1		409	88.0±15.6	
Exercise(times/week)						
0	1197	93.2±15.5		901	88.2±16.5	
1-4	299	97.1±15.9	0.000	139	92.1±14.8	0.004
≥5	137	96.5±16.2		202	92.0±15.9	
Dietary calcium intake						
Q_1	326	94.7±15.8		234	89.4±17.4	
Q_2	313	93.8±14.7	0.693	262	89.7±15.7	0.749
Q_3	304	93.5±16.6		245	88.8±15.9	
Q_4	311	94.7±15.9		226	90.5±15.4	
Dietary protein intake						
Q_1	189	93.5±16.1		214	88.8±17.6	
Q_2	287	93.4±15.7	0.586	250	89.3±16.0	0.348
Q_3	362	94.9±15.6		259	91.1±15.2	
Q_4	416	94.4±15.7		244	88.9±15.7	

Table 3-3. Multiple linear regression analysis for bone stiffness in men

Variables	Men(40≤age≤59)		Men(60≤age≤70)	
	β	*P*	β	*P*
Age(years)	-0.074	0.002	-0.021	0.080
BMI(kg/m^2)	0.091	0.000	0.154	0.000
Any chronic disease	-0.033	0.624	0.005	0.652
Smoking(pack-years)	-0.055	0.056	-0.098	0.010
Alcohol consumption(g/day)	0.025	0.754	-0.034	0.872
Exercise(times/week)	0.085	0.000	0.034	0.025
Dietary calcium intake(mg/day)	-0.110	0.987	0.025	0.954
Dietary protein intake(g/day)	-0.156	0.009	0.096	0.124

C. Factors affecting the bone stiffness among women

Table 4-1 shows baseline characteristics of the premenopausal and postmenopausal women. Mean BMI, years at menarche and numbers of children were significantly higher in postmenopausal women than in premenopausal women, while the proportions of subjects who drink alcohol and exercise regularly were significantly higher in pre-menopausal women.

Table 4-1. Distribution of potential risk factors by menopause status in women

	Premenopausal women (*n*=1294)	Postmenopausal women (*n*=2802)
BMI(kg/m^2)**	24.6±3.38	24.9±3.42
Any chronic disease(%)***	53.8	69.8
Current smokers(%)	1.0	1.6
Current drinkers(%)***	33.9	23.1
Alcohol consumption(g/day)***	4.46±17.1	2.40±12.1
Regular exercise(%)*	28.7	25.4
Dietary calcium intake(mg/day)***	465.6±280.8	417.3±273.4
Dietary protein intake(g/day)***	58.0±23.9	51.6±22.4
Menarche(years)***	15.9±1.85	16.8±1.86
No. of children***	2.5±1.04	3.6±1.6

* p<0.05; ** p<0.01; ***p<0.001

Table 4-2 shows the mean bone stiffness values of potential risk factors by menopause status in women. There was positive linear trend of BMI with bone stiffness, in contrast, there was a negative association between bone stiffness and parity. In premenopausal women who drank light to moderate amounts of alcohol had higher level of bone stiffness than those who did not drink. However, the majority of various lifestyle characteristics including exercise habits and dietary intake, and menstrual history did show significant results in post-menopausal women. In addition, the subjects who reported to have used estrogen replacement therapy showed significant higher level of bone stiffness than those who never undergone.

In multivariate regression analysis of female, BMI, time spent exercise and dietary protein intake in premenopausal, and years since menopause, BMI, estrogen replacement therapy and numbers of parity in postmenopausal were significantly correlated with bone stiffness (Table 4-3).

Table 4-2. Mean bone stiffness values of potential risk factors by menopause status in women

Variable	Premenopausal women			Postmenopausal women		
	n	Mean±SD	*P*	*n*	Mean±SD	*P*
BMI						
underweight	60	89.4±15.2		133	77.8±14.0	
normal	677	91.3±13.6	0.000	1329	80.6±14.4	0.031
overweight/obese	531	94.8±14.1		1285	81.2±14.6	
Any chronic disease						
no	584	92.8±13.9	0.712	826	80.8±13.8	0.812
yes	676	92.5±14.1		1890	80.7±14.8	
Postmenopausal estrogen						
no				2135	80.2±14.5	0.000
yes				338	83.8±13.8	
Smoking status						
no	1253	92.7±14.0	0.538	2702	80.8±14.5	0.161
yes	13	90.3±10.4		44	77.7±11.2	
Drinking status						
no	837	92.4±14.3	0.432	2108	80.5±14.4	0.141
yes	426	93.1±13.2		636	81.5±14.7	
Alcohol consumption(g/day)						
0	837	92.4±14.3		2108	80.5±14.4	
≤15	328	93.8±13.2	0.044	501	81.7±14.8	0.175
>15	84	89.6±12.6		105	79.7±14.8	
Exercise(times/wk)						
0	898	92.4±13.6		2050	80.1±15.6	
1-4	242	92.3±14.1	0.170	329	84.2±14.0	0.000
≥5	123	94.9±15.8		355	81.6±13.9	

Table 4-2. Continued

Variable	Premenopausal women			Postmenopausal women		
	n	Mean±SD	*P*	*n*	Mean±SD	*P*
Dietary calcium intake						
Q_1	179	91.8±12.7		525	78.8±13.4	
Q_2	208	92.5±14.9	0.217	533	79.7±15.4	0.000
Q_3	257	92.5±14.5		497	82.0±14.8	
Q_4	284	94.3±13.8		505	81.8±14.0	
Dietary protein intake						
Q_1	185	91.2±12.1		631	78.4±14.8	
Q_2	232	93.5±15.3	0.083	573	80.4±14.7	0.000
Q_3	239	92.1±14.3		457	82.2±14.2	
Q_4	272	94.3±13.9		399	82.3±13.4	
Menarche(years)						
≤15	538	92.6±14.3		606	81.9±14.3	
16-18	603	92.7±13.3	0.983	1572	80.9±14.5	0.012
>18	101	92.7±15.6		470	79.3±14.0	
No. of children						
0	29	97.1±17.0		54	79.8±15.3	
1-2	730	93.2±13.1	0.048	607	84.5±14.0	0.000
≥3	508	91.7±14.9		2087	79.7±14.4	
Menstrual duration(years)						
≤45				478	78.7±14.7	0.020
46-50				946	80.6±14.1	
>50				466	81.2±13.9	
Years since menopause						
≤5				854	86.2±13.5	
6-10				557	81.1±13.5	0.000
11-15				389	77.2±13.5	
>15				579	75.1±14.1	

Table 4-3. Multiple linear regression analysis for bone stiffness in women

Variables	Premenopausal women		Postmenopausal women	
	β	P	β	P
Age(years)	-0.013	0.562		
Years since menopause			-0.244	0.000
BMI(kg/m^2)	0.118	0.000	0.056	0.006
Any chronic disease	-0.013	0.563	0.015	0.423
Postmenopausal estrogen			0.048	0.046
Smoking status	-0.013	0.856	-0.023	0.741
Alcohol consumption(g/day)	0.000	0.623	0.023	0.825
Exercise(times/week)	0.091	0.009	0.007	0.072
Dietary calcium intake(mg/day)	-0.109	0.924	0.052	0.915
Dietary protein intake(g/day)	-0.181	0.010	0.103	0.324
Menarche(years)	-0.013	0.126	0.019	0.246
No. of children	-0.045	0.078	-0.074	0.005

IV. DISCUSSION

Osteoporosis is a disease of fragility fractures related to decreased bone density and poor bone quality. Until now, considerable knowledge has been accumulated on the impact factors of bone health in Caucasian populations, whereas such knowledge is still insufficient in Asian populations, especially in Korean. In this study we measured calcaneal QUS measures such as bone stiffness in a large general population including men and premenopausal women (the subjects of most studies were postmenopausal women). This will help us to understand the bone status of all genders in Korean adults. In the QUS measurement, BUA is determined mainly by the scatter of the sound waves and reflects the spatial orientation of the bone trabeculae, whereas SOS is related to the ultrasound velocity and assumed a constant heel thickness. Many studies have suggested that bone stiffness identifies patients with osteoporotic fractures better than BUA or SOS and that index of bone stiffness presents greater precision (Lees and Stevenson, 1993; Yamazaki et al., 1994; Hadji et al., 1999; Mikhail et al., 1999). Moreover, Hans et al. (1996) pointed out that bone stiffness could be used as a single index to predict the fracture risk. Therefore, we used the bone stiffness value to predict the fracture risk of Korean adults.

Bone is a living tissue. It is constantly resorbed and formed in the process known as remodelling. Thus, bone formation takes place not only during growth but throughout life. Osteoblasts are the cells responsible for bone formation and resorption. During growth, bone formation exceeds bone resorption. From age thirty to age fifty, the

amount of bone formed approximately equals the amount resorbed. From the menopause in women and from about the sixth decade in men, bone resorption starts to exceed bone formation. The mass of bony tissue present at any time during adult life is the difference between the amount accumulated at maturity, i.e. the so-called peak bone mass, and that lost with aging (Genant et al., 1999). In present study, the bone stiffness values gradually decreased with age in men and women. With the linear regression equation, the mean decreasing rate of bone stiffness in women was 2.6-fold that of men (0.447% per year, and 0.171% per year, respectively). These results are not consistent with previous studies (Table 1). For example, the total age-related decreasing rate for bone stiffness in women was lower than that of Italian women but higher than that of Chinese women. The decreasing rate for bone stiffness in men was higher than that of Italian and Chinese men. This difference could be accounted for by multiple factors such as body size, lifestyle, nutritional and racial differences.

We found a significant correlation between bone stiffness and body size (BMI) in both sexes. In the multiple linear regression analysis, including age, BMI appeared to be the more important influencing factor of bone stiffness in both sexes, which is in agreement with many reports, including studies on BMD (Yeh et al., 2004; Kirchengast et al., 2002; Kao et al., 1994; Nishizawa et al., 1991). Body weight is believed to exert a beneficial effect on bone tissue in terms of osteoporotic risk. The skeleton responds to mechanical loading, resulting in increased bone mass and density (Korpelainen et al., 2003). Interestingly, changes in body composition with increasing age differ between people in Western and Asian countries. Based on a large-scale

Western study involving subjects aged from 45 to 75 years (Kyle et al., 2005), body fat mass in both men and women increased with age. However, both lean body and fat mass decrease with age on the Korean population (Lim et al., 2004). Therefore, it is recommended to maintain an appropriate weight, to maintain the balance between bone absorption and bone formation in elderly Korean men and women.

In this study, exercise has a strong impact on bone stiffness in men and premenopausal women, while this effect disappeared in post-menopausal women. In a cross-sectional study such as present study, it is difficult to directly address the difference in the effect of exercise on bone stiffness between pre- and postmenopausal women, though it could be explained that body composition and circulating estrone levels may exert. Several prospective studies that investigated the effect of exercise on bone mineral density have also been published. Nelson et al. (1994) demonstrated positive exercise effects on the bone mineral density of the femoral neck and the lumbar spine. In contrast, some prospective studies (Blumenthal et al., 1991; Pruitt et al., 1995) reported that exercise increased muscular strength but not bone mineral density of lumber spine or hip. The mechanisms by which exercise increases bone stiffness are poorly understood, however it may be the stimulation of bone mineralization by mechanical forces placed on the bones during exercise.

Cigarette smoking has been recognized as one of the deleterious factors in bone metabolism. Seeman and Melton (1983) first reported that tobacco consumption increased the incidence of vertebral fractures in men. A meta-analysis reported that smoking increases the lifetime risk of developing a vertebral fracture by 32% and a hip fracture by

40% in men. It appears that smoking has an independent, dose-dependent effect on bone loss, which increases fracture risk (Ward and Klesges, 2001). Several studies found smoking was a factor affecting BMD mostly in elderly men (Lau et al., 2006; Vogel et al., 1997; Orwoll et al., 2000). In this study, we observed a negative correlation between accumulated cigarette smoking (pack-years) and bone stiffness among men aged 60-70 years after adjustment of BMI and physical activity.

Relationship between alcohol consumption and osteoporosis from previous studies are somewhat conflicting. 'Binge' alcohol consumption leading to intoxication may affects the risk of falling. Also very heavy and sustained levels of alcohol consumption are associated with poor nutrition. Laitinen et al. (1991) first reported a positive correlation between alcohol intake and BMD, with a 12%, 15%, and 9% increase at lumbar spine, Ward's triangle, and femoral neck, respectively; changes in values for the spine and Ward's triangle were significant. Cawthon et al. (2006) reported moderate to heavy users of alcohol ($\geq$ 25.6g/day) had a multivariate adjusted mean BMD of 0.981 g/cm^2 at the total hip, whereas non-drinkers had an adjusted mean BMD of 0.948 g/cm^2. However, in Cardiovascular Health Study (Mukamal et al., 2007), alcohol intake was shown to have a significant U-shaped relationship with risk of hip fracture, with an approximately 20% lower risk for consumers of up to 13 drinks per week than for non-drinkers, even after multivariable adjustment. The pathogenesis of increased bone density with alcohol consumption has not been established, but it may be suggested that alcohol promotes the production of adrenal androstenedion and increases the conversion to estrogen. We did not

find, in the multiple regression analysis, any significant association between alcohol consumption and bone stiffness. This may be due to Koreans drink irregularly in social setting, self-reported alcohol consumption may be underestimated and the actual amount and frequency of alcohol consumed by these subjects may differ from that reported.

Calcium is one of the main bone-forming minerals and appropriate supply to bone is essential at all stages of life. Many studies suggested an increased risk of hip fracture with decreased calcium intake (Lau et al., 1988; Holbrook et al., 1988; Johnell et al., 1995; Kanis et al., 1999). Studies in Southern Europe observed that the greatest risk of fracture was amongst those with the lowest consumption of milk and cheese, indicative of a very low calcium intake (Johnell et al., 1995; Kanis et al., 1999). In contrast, we were unable to find any association between the calcium intake and stiffness values. In populations with a moderate-high risk of osteoporosis, case-control and cohort studies in countries with an average calcium intake close to recommended levels have shown no relationship between calcium intake and risk of hip fracture (Kreiger et al., 1992; Cummings et al., 1995; Wickham et al., 1988; Cooper et al., 1988; Cumming et al., 1994). Moreover, calcium intake was not a determinant of longitudinal bone loss over 4 years in the Framingham cohort of older people from the USA (Hannan et al., 2000). Thus, it can be suggested that calcium intake might be responsible for the apparent difference in bone mass among different population.

On a world-wide basis, high protein intakes have been linked with hip fracture because the consumption of protein, particularly in the form

of meat and dairy products, is greatest in countries where hip fractures are common (Abelow et al., 1992). Protein intake is a determinant of urinary calcium excretion, and animal protein, which is rich in sulphur-containing amino acids, contributes to an acidic environment. There are concerns, therefore, that high protein intakes, especially those rich in animal protein, are inadvisable for long-term bone health (Prentice. 2004). Our study indicates that dietary protein intake also has a negative effect on bone stiffness in younger population. Conversely, a low protein intake in the elderly may contribute to the risk of osteoporotic fracture. A substantial proportion of elderly patients in Western countries show signs of clinical protein-energy malnutrition on admission (Mowe et al., 1994; Larsson et al., 1990). Falls are more likely in older people with malnutrition (Lipschitz, 1995) and patients with hip fracture have less bone loss and require hospitalisation for shorter periods when given protein supplementation (Schurch et al., 1998). As described above, a low protein intake was associated with the greatest bone loss over 4 years in the Framingham cohort (Hannan et al., 2000). At present, there is no firm evidence of optimal protein intake for the prevention of bone health.

In this study, the postmenopausal women who reported to have used estrogen replacement therapy showed significantly higher bone stiffness values than who have not used, even after adjustment of BMI and years since menopause. The Women's Health Initiative, have demonstrated clearly that estrogen replacement can increase bone mass approximately 2% per year and decrease the risk of hip and spine fracture by approximately 35% (Rossouw et al., 2002). Estrogen use had a very strong effect on bone stiffness, thus confirming the results

found in the ESOPO study (Adami et al., 2003).

We found a negative association between stiffness and parity. The relationship between parity and bone mass has yielded mostly negative results, though two studies (Sowers et al., 1992; Fox et al., 1993) showed a protective effect. However in these two studies, only nulliparous women were compared with parous women and it is possible that the nulliparous state may reflect a hormone environment of both sterility and low bone mineralization. It is worth mentioning that the relationship between stiffness and parity we found was stronger when nulliparous women were excluded (not shown here).

Our study has several limitations. First, the study is cross-sectional rather than longitudinal, which might not be suitable for revealing detailed causation or reverse causation between risk factors and bone health. Second, assessment depending on recall by the participants cannot exclude the possibility of measurement error. Despite these limitations, this study includes largest sample size of the general population, ever investigated in Korea. This is also a first epidemiologic study of risk factors for bone status in both genders.

In conclusion, the decreasing rate of bone stiffness with age are higher in women than in men. Secondly, BMI and physical activity were associated positively with bone stiffness in both men and women, but age, amount of cigarettes smoking and dietary protein intake in men, and dietary protein intake, number of parity and years since menopause in women were associated negatively with bone stiffness.

Some recommendations can be drawn: a) Maintain a BMI of not less than 20kg/m^2. b) Avoid smoking, particularly among the elderly men. c) Maintain a physically active status. d) Limit protein intake, especially

among younger population. Ignorance about osteoporosis is still common among health professionals, patients and the public. Therefore, education should target all of these groups. The aim of an extensive education and communication programme is may be increasing the knowledge of bone physiology and osteoporosis, raising the awareness about major risk factors, prevention and management of the disease.

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